c) the antisense oligonucleotide does not contain (i) four or more consecutive elements capable of forming three hydrogen bonds each with four consecutive cytosine bases (CCCC) within the target nucleic acid sequence or (ii) four or more consecutive elements of GGGG within the target nucleic acid sequence,

d) the antisense oligonucleotide does not contain (i) two or more series of three consecutive elements capable of forming three hydrogen bonds each with three consecutive cytosine bases (CCC) within the target nucleic acid sequence or (ii) two or more series of three consecutive elements of GGG within the target nucleic acid sequence, and

F 1 cont'd

e) the ratio of residues forming two hydrogen bonds each with the target nucleic acid sequence with respect to residues forming three hydrogen bonds each with the target nucleic acid sequence is

$$\frac{\text{3H-bond-R}}{\text{3H-bond-R} + \text{2H-bond-R}} \geq 0.29$$

wherein

- 3H-bond-R = residues forming three hydrogen bonds per residue and
- 2H-bond-R = residues forming two hydrogen bonds per residue,

– generating the designed antisense oligonucleotide, and

– synthesizing the generated antisense oligonucleotide.

53. The method according to claim 52, wherein the ratio

$$\frac{\text{3H-bond-R}}{\text{3H-bond-R + 2H-bond-R}} = 0.33 \text{ to } 0.86.$$

54. The method according to claim 52, wherein the generated antisense oligonucleotide is modified for higher nuclease resistance than naturally occurring oligo- or polynucleotides.

F-1 cont'd

55. The method according to claim 54, wherein the generated antisense oligonucleotide is modified at the bases, the sugars or the linkages of the oligonucleotides, preferably by phosphorothioate (S-ODN) internucleotide linkages, and/or methylphosphonate internucleotide linkages, N'3 -> P5' phosphoramidate linkages, peptide linkages or 2'-methoxyethoxy modifications of the sugar or modifications of the bases.

56. The method according to claim 55, wherein the antisense oligonucleotide has at least two different types of modifications.

57. The method according to claim 52, wherein the antisense oligonucleotide is covalently linked with folic acid, a hormone, or a derivative thereof.

58. The method of claim 52 wherein the antisense oligonucleotide is modified with steroid hormones, corticosteroids, peptides, proteoglycans, glycolipids, or phospholipids.

59. The antisense oligonucleotide produced by the method according to claim 52 excluding oligonucleotides represented by SEQ ID NOS: 826-1272.

60. The antisense oligonucleotide of claim 59 that does not contain

a) four or more consecutive guanosine (N_aGGGGN_b) or inosine (N_aIIIIN_b) residues,

b) two or more series of three or more consecutive guanosine residues ($N_aGGGN_cGGGN_b$),

c) two or more series of three or more consecutive inosine residues ($N_aIIIN_cIIIN_b$),

wherein N_a, N_b, N_c represent independently nucleotides or oligonucleotides or derivatives thereof having 0 to 20 residues.

F1 cont'd

61. The antisense oligonucleotide of claim 59 comprising a minimum of ten elements sand a maximum of 41 elements capable of forming either two or three hydrogen bonds per element.

62. The antisense oligonucleotide according to claim 59 having modifications at the bases, the sugars or the phosphate moieties of the oligonucleotides.

63. The antisense oligonucleotide of claim 59, wherein the modifications are phosphorothioate (S-ODN) internucleotide linkages, and/or methylphosphonate internucleotide linkages, N'3 -> P5' phosphoramidate linkages, peptide linkages or 2--methoxyethoxy modifications of the sugar or modifications of the bases.

64. The antisense oligonucleotide of claim 59, coupled to or mixed with folic acid, hormones, steroid hormones such as oestrogene, progesterone, corticosteroids, mineral corticoids, peptides, proteoglycans, glycolipids, phospholipids and derivatives therefrom.

F 1 cont'd

65. The antisense oligonucleotide according to claim 59, wherein the antisense oligonucleotide against the TGF-β1 gene comprise SEQ ID NOS: 41 to 73, the oligonucleotides against the gene p53 comprise SEQ ID NOS: 74 to 106, the antisense oligonucleotides against junB comprise SEQ ID NOS: 154 to 172 , the antisense oligonucleotides against junD comprise SEQ ID NOS: 173 to 203 , the antisense oligonucleotides against the erbB-2 gene comprise SEQ ID NOS: 298 to 380 , the antisense oligonucleotides against c-fos genes comprise SEQ ID NOS: 476-506; the antisense oligonucleotides against the gene TGF-β2 comprise SEQ ID NOS: 519 to 556 as well as the antisense oligonucleotides against the gene rb comprise SEQ ID NOS: 597 to 641, as well as SEQ ID NOS: 1273 to 1764.

66. A composition comprising the antisense oligonucleotide according to claim 59 for the manufacturing of a medicament or a composition for the inhibition of the genes p53, rb, junD, junB. TGF-β1, TGF-β2 to influence cell proliferation, in particular of primary cell cultures such as liver cells, kidney cells, osteoclasts, osteoblasts and/or keratinocytes and/or cells of the blood lineage, such as bone marrow stem cells, and/or progenitor cells of red and white blood cells.

F1 cont'd

67. A medicament comprising the antisense oligonucleotide according to claim 59 together with additives.

68. The use of the antisense oligonucleotide according to claim 59 for the preparation of a medicament for the prevention or the treatment of neoplasm, hypoproliferation, hyperproliferation, degenerative diseases, neurodegenerative diseases, ischaemia, disorders of the immune system and/or infectious diseases, and/or metabolic dysfunctions.

69. The use of the antisense oligonucleotide according to claim 59 for the analysis of gene function or drug target validation.

REMARKS

New claims 52-69 are submitted, hereby, in place of claims 35-51. Claims 52-68 represent the subject matter of claims 35-51, revised to more clearly define the instant invention.